Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy

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Abstract: BACKGROUND: This prospective multicenter study assessed the prognostic influence of the extent of resection when compared with biopsy only in a contemporary patient population with newly diagnosed glioblastoma. PATIENTS AND METHODS: Histology, O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, and clinical data were centrally analyzed. Survival analyses were carried out with the Kaplan-Meier method. Prognostic factors were assessed with proportional hazard models. RESULTS: Of 345 patients, 273 underwent open tumor resection and 72 biopsies; 125 patients had gross total resections (GTRs) and 148, incomplete resections. Surgery-related morbidity was lower after biopsy (1.4% versus 12.1%, P = 0.007). 64.3% of patients received radiotherapy and chemotherapy (RT plus CT), 20.0% RT alone, 4.3% CT alone, and 11.3% best supportive care as an initial treatment. Patients 60 years with a Karnofsky performance score (KPS) of 90 were more likely to receive RT plus CT (P < 0.01). Median overall survival (OS) (progression free survival; PFS) ranged from 33.2 months (15 months) for patients with MGMT-methylated tumors after GTR and RT plus CT to 3.0 months (2.4 months) for biopsied patients receiving supportive care only. Favorable prognostic factors in multivariate analyses for OS were age 60 years [hazard ratio (HR) = 0.52; P < 0.001], preoperative KPS of 80 (HR = 0.55; P < 0.001), GTR (HR = 0.60; P = 0.003), MGMT promoter methylation (HR = 0.44; P < 0.001), and RT plus CT (HR = 0.18, P < 0.001); patients undergoing incomplete resection did not better than those receiving biopsy only (HR = 0.85; P = 0.31). CONCLUSIONS: The value of incomplete resection remains questionable. If GTR cannot be safely achieved, biopsy only might be used as an alternative surgical strategy.

DOI: https://doi.org/10.1093/annonc/mdt388

Article type: Original Article, Clinical study

Title: Gross total but not incomplete resection of GBM prolongs survival in the era of radiochemotherapy

Running title: Extent of resection and *MGMT* promoter methylation in glioblastoma

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Counts: Number of characters: Title: 94/ Running Head: 65 **// Number of words:** Abstract: 244 / Manuscript: 2110 **// Numbers of References:** 22 **// Numbers of figures / tables in main manuscript:** 2 / 3. **Number of supplement figures/ tables:** 2/1

Abstract

Background: This prospective multicenter study assessed the prognostic influence of extent of resection as compared to biopsy only in a contemporary patient population with newly diagnosed glioblastoma.

Patients and methods: Histology, O^6-methylguanine-DNA methyltransferase (*MGMT)* promoter methylation status and clinical data were centrally analysed. Survival analyses were performed with the Kaplan-Meier method. Prognostic factors were assessed with proportional hazards models.

Results: Of 345 patients, 273 underwent open tumor resection and 72 biopsies; 125 patients had gross total resections (GTR) and 148 patients incomplete resections. Surgery-related morbidity was lower after biopsy (1.4% vs. 12.1%, p=0.007). 64.3% of patients received radiotherapy (RT) plus chemotherapy (CT), 20.0 % RT alone, 4.3% CT alone, and 11.3% best supportive care as initial treatment. Patients ≤ 60years and with a Karnofsky performance score (KPS) ≥ 90 were more likely to receive RT plus CT (p<0.01). Median OS (PFS) ranged from 33.2 months (15.0 months) for patients with *MGMT* methylated tumors after GTR and RT plus CT to 3.0 months (2.4 months) for biopsied patients receiving supportive care only. Favorable prognostic factors in multivariate analysis for OS were age ≤ 60 years (HR=0.52; p<0.001), preoperative KPS ≥ 80 (HR=0.55; p<0.001), GTR (HR=0.60; p=0.003), *MGMT* promoter methylation (HR=0.44; p<0.001), and RT plus CT (HR=0.18, p<0.001); patients undergoing incomplete resection did not better than those receiving biopsy only (HR=0.85; p=0.31).

Conclusions: The value of incomplete resection remains questionable. If GTR cannot be safely achieved, biopsy only might be used as an alternative surgical strategy.

Key words: Glioblastoma, *MGMT*, prognosis, extent of resection, biopsy, temozolomide

Abbreviations

CT, chemotherapy; EOR, extent of resection; GTR, gross total resection; HR, hazard ratio; KPS, Karnofsky performance score; *MGMT*, O^6 methylguanine-DNA methyltransferase; MSP, methylation-specific PCR; OS, overall survival; PFS, progression-free survival; RT, radiotherapy, TMZ, temozolomide; WHO, World Health Organization

Introduction

Glioblastoma is the most frequent and most aggressive primary brain tumor in adults [1]. Combined radio- and chemotherapy (RT plus CT) has become the standard of care [2] and has significantly improved the prognosis particularly for tumors exhibiting a methylated promoter of the gene encoding O^6-methylguanine-DNA methyltransferase (*MGMT*) [3]. Gross total resection (GTR) before adjuvant treatment has also been shown to gain favorable impact on outcome [4-6]. In contrast, the prognostic place of incomplete resection as compared to biopsy only is not yet clearly defined [2]. The elucidation of this question is important since GTR cannot be always achieved [7, 8].

This multicenter observational study was conducted to identify prognostic factors in glioblastoma patients treated according to current standards of care. Based on our previous analysis on non-resectable glioblastomas demonstrating surprisingly long survival after biopsy only in the era of RT plus CT [9], we awaited similar survival rates after incomplete resection and biopsy only.

Patients and Methods

Study Design

The German Glioma Network (GGN) has generated a prospective longitudinal database to follow patients with newly diagnosed glioblastoma. Patients were recruited from October 2004 until March 2009; data base closure was March 2012. All patients gave informed consent. Data collection at enrolment and follow-up addressed important patient-, tumor-, and treatment-related parameters including *MGMT* promoter methylation status. The extent of open resection (EOR) was determined locally by early (<72 h) postoperative MRI and scored according to the study of Stummer et al. either as GTR (no residual contrast enhancement in T_1-weighted sequences) or incomplete resection (any contrast-enhancement with a volume of

more than one voxel in the T_1-weighted images) [10]. Prospective estimations of EOR were done in a blinded fashion. No additional volumetric analyses were performed. Central histological review according to the World Health Organization (WHO) [1] was done at the Department of Neuropathology, University of Bonn. Central determination of the *MGMT* promoter methylation status by methylation-specific PCR [3] was performed at the Department of Neuropathology, Heinrich Heine University Düsseldorf. Data were centrally collected and analysed (Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig). Treatment decisions were independently rendered at each academic center. Tumor progression was assessed according to the Macdonald criteria [11].

Statistical analysis

Associations of clinical data were tested by χ^2 test, Fisher's exact test, and Mann-Whitney-U test. Suvival data were analyzed with the Kaplan-Meier method. Reference point was the date of first surgery. The log-rank test was used to compare outcome data. Multivariate analysis was performed with Cox regression models. p values ≤ 0.05 were considered as statistically significant. Statistical analyses were performed using IBM SPSS (Version 20.0.0).

Results

A total of 345 patients were analysed. Clinical data of the study population are summarized in Table 1. Sixty-two patients were older than 70 years and 28 patients had a Karnofsky performance score (KPS) below 70. GTR**,** incomplete resection, and biopsy were done in 125 patients, 148 patients, and 72 patients, respectively. Biopsied patients were older (median: 65 vs. 60 years; p=0.008), rated similarly on the performance scale (median KPS: 80 each, p=0.5), and had similarly often an eloquent tumor location (23.6% versus 19.4%; p=0.4) as compared to patients undergoing incomplete resection. The frequency of an eloquent tumor

location was lowest in the GTR-group (14.4%; p=0.04). Transient complication occurred in 33 patients after resection and in one patient after biopsy (p=0.007). Histopathological diagnosis revealed 329 glioblastomas, 9 giant cell glioblastomas, and 7 gliosarcomas. A methylated *MGMT* promoter was found in 48.1% of the study cohort. Methylated and unmethylated tumors did not differ in terms of age (median: 60 vs. 62 years; p=0.4), KPS (median: 80 each, p=0.3), EOR (p=0.8), or mode of first-line treatment (p=0.8).

64.3% of the study population patients underwent RT plus CT. RT alone, CT alone, and supportive treatment were applied in 20.0%, 4.3%, and 11.3%, respectively. Patients ≤ 60 years (odds ratio 3.3, 95%-CI 2.1-5.3) and patients with KPS ≥ 90 (odds ratio 3.0, 95%-CI 1.8-4.8) were more likely to receive RT plus CT. Biopsied patients were less frequently treated with RT plus CT (odds ratio 0.5, 95% CI 0.3-0.8) and received more often supportive care only (odds ratio 2.4, 95% CI 1.2-4.9).

Treatment results and prognostic/predictive factors

Overall, 327 patients suffered from tumor progression and 310 patients deceased during the follow-up period. Median PFS was 6.4 months and median OS was 12.8 months. Outcome stratified for EOR as compared to biopsy, first-line treatment, and *MGMT* methylation status is given in Table 2: Outcome was best in case of RT plus CT (median PFS: 7.8 months/ median OS: 17.1 months) and worst after supportive treatment (median PFS: 2.7 months/ median OS: 3.0 months; supplement Figure S1). GTR was associated with superior OS (median: 17.1 months; p=0.001); OS after incomplete resection was not better than after biopsy only (median: 11.7 vs. 8.7 months; p=0.1; Figure 1). PFS was not influenced by EOR as compared to biopsy only. *MGMT* promoter methylation was associated with superior PFS (median: 7.6 vs. 5.8 months) and OS (median: 21.0 vs. 11.0 months) (each p<0.001; Figure 1).

Subgroup analysis of patients after RT plus CT (*N*=222) revealed similar results (Figure 2): GTR was associated with prolonged OS (median: 21.0 months; *p*=0.034) whereas OS after incomplete resection and biopsy was similar (median: 15.2 vs. 15.7 months; *p*=0.4)**.** Survival was best in *MGMT* methylated tumors undergoing GTR (median PFS: 15.0 months/ median OS: 33.2 months). Median PFS (OS) of biopsied, methylated tumors was 12.0 (26.2) months, which compared favorably with that of unmethylated tumors after GTR (5.7 (14.4) months; Table 2; supplement Figure S2).

Cox models

One-variable models are given in supplement Tables S1. Multivariate Cox regression analyses of both the overall population and the subpopulation receiving RT plus CT revealed similar results: Favorable prognostic factors for OS were age ≤ 60 years, KPS ≥ 80, GTR, *MGMT* promoter methylation, and RT plus CT; incomplete resection was not better than biopsy (Table 3).

Discussion

The highly invasive growth characteristics of glioblastomas explain that curative surgical treatment cannot be achieved [1]. Nevertheless, beneficial cytoreductive effects of GTR have been reported, which is defined as complete resection of the contrast-enhancing tumor parts [6, 12, 13]. According to more recently published prospective randomized data, GTR can be expected to be achieved in 40% of glioblastoma patients [14]. The majority of glioblastoma patients still undergo incomplete resection and some of them receive biopsy only, which is due to diffuse tumor extension, affection of functional relevant areas, patient-related risk factors (such as increased age and co-morbidity), or any combination of these factors [9, 15]. Surprisingly, the prognostic impact of incomplete resection as compared to biopsy only

remains unclear. The traditional view is that GTR is better than incomplete resection and the latter better than biopsy [2, 16]. A few studies, however, that have addressed this issue, did not analyze EOR by early postoperative MRI, did not control for the effect of *MGMT* promoter methylation and applied treatment strategies, and/or were seriously biased due to the influence of other prognostic factors (in favor of the resection group) [16, 17]. The current prospective observational study, which analyzed outcome measurements of a large and unselected patient population collected in six academic centers with a dedicated focus on neuro-oncology, goes one step beyond these limitations: Outcome measurements were adjusted for the effects of *MGMT* promoter methylation and other important patient-, tumor-, and treatment related factors. Patients undergoing biopsy only were used as a reference group for prognostic evaluation of open tumor resection. This approach overcomes selection bias, which always occurs when comparing surgery responders (GTR) with non-responders (incomplete resection) [18]. It was remarkable that the pre-treatment prognostic profile of the biopsy and the incomplete resection groups was not as different as usually found [16, 17]: Patients of the biopsy group were only slightly older, did not rate worse on the KPS scale and did not exhibit higher frequencies of eloquent tumor locations than those undergoing incomplete resection. Hence, patients in these two groups were relatively well balanced. It was noteworthy, however, that biopsied patients were less likely to receive RT or RT plus CT in this series.

In accordance with other data we found GTR to prolong OS [5, 6, 12, 16]. A prognostic impact of incomplete resection, however, could not be detected: Incomplete resection did not provide advantages with respect to OS as compared to biopsy alone. This was demonstrated in both the full analysis and the subgroup analysis set of patients treated with RT plus CT. The latter analysis was performed to account for the described treatment related imbalances in the full analysis set: still existing but not significant differences in OS between biopsied

and incompletely resected patients in the full analysis set resolved nearly completely in the subgroup analysis.

Beyond RT plus CT, *MGMT* promoter methylation turned out to be the most powerful factor influencing OS. Outcome in biopsied, *MGMT* methylated tumors was better than in tumors lacking *MGMT* promoter methylation after GTR and RT plus CT. The study results confirmed previously reported surprisingly long OS of biopsied GBM patients after combined treatment in case of a methylated *MGMT* promoter [9]. Apparently, tumors' biology by far outweights the prognostic impact of resective surgery. The prognostic models did not indicate interactions between the influence of EOR as compared to biopsy and *MGMT* promoter methylation status. Surgery was not more effective in unmethylated or methylated tumors.

EOR was dichotomized in the current report: Those exhibiting any gadolinium enhanced volume on their early post-operative MRI were classified as incomplete resection. The chosen classification scheme is supported by the results of the post-hoc evaluation of the prospective randomized data by Stummer et al. [6]: no distinct survival rates were found for subgroups undergoing different degrees of EOR; only those receiving GTR did significantly better. Since we considered these data as the currently most convincing ones for prognostic evaluation of EOR, the current study protocol was designed accordingly.

Retrospective comparison of tumor size pre- and post-operatively has proposed a linear increase between EOR and survival beyond a threshold of approximately 78% in one more recently pusblished study [19]. The authors, however, have described overlapping subpopulations regarding EOR (>78%, >80%, >90% etc.) and it remains therefore unclear to which extent the applied top-down threshold calculation has been biased by those undergoing complete or nearly complete resection. Our data did not support those assumptions: For those undergoing RT plus CT, the prognostic impact of GTR was only moderate as compared to

biopsy only. Thus, the existence of true prognostic relevant thresholds in addition to GTR seems to be unlikely. The provided prognostic models of this study rather indicate non-linear correlations between EOR and outcome.

The proponents of linear correlations between EOR and outcome are confronted with so far unresolved methodological problems: A proper identification of thresholds in addition to GTR demands non-overlapping subgroups exhibiting distinct degrees of EOR. Thus, large multi-institutional studies are necessary to analyze the interesting idea of a resection threshold for glioblastoma patients. Additionally, volumetric estimation of post-surgical MRI scans has been shown to suffer from low inter-observer agreement [20, 21].

Apparently two different classes of glioblastoma patients exist: Those harboring resectable tumors (which should be resected) and those harboring unresectable ones, which do not need partial “debulking” unless decompressive surgery of pronounced and symptomatic space occupying lesions is necessary [22]. This conclusion is important for the patient and the treating oncologist: Surgery-related complications of potentally superfluous incomplete resection might delay the initiation of adjuvant treatment, decrease quality of life, and comprise outcome [7, 15]. Even though in the current series, the complication rate after open tumor resection was in the lower range of reported data in the literature [15], it was still ten-times higher than after biopsy.

We did not find any prognostic impact of open tumor resection on PFS. Estimation of PFS, however, might be biased in unfavor of the resection group particularly in case of GTR, as usually the appearance of any new lesion after GTR is classified as tumor recurrence; in contrast, a 25% increase of tumor volume is required for indication of tumor progression after incomplete resection or biopsy [11].

In summary, we found a moderate favorable prognostic effect of GTR in the era of RT plus CT. The efficacy of GTR was not influenced of *MGMT* promoter methylation, which turned out to be the most powerful pre-treatment factor for OS and PFS. In contrast, the prognostic value of incomplete resection as compared to biopsy only remains questionable. The indication of biopsy should be reconsidered for unresectable tumors, as biopsy can be safely performed and enables adequate histological diagnosis and determination of the *MGMT* promoter methylation status even in patients e. g. with eloquent tumors.

Acknowledgements

Special thanks to all clinical coordinators, the study nurses and all other co-workers involved in the GGN especially at the six academic centres at the Universities of Bonn, Dresden, Freiburg, Hamburg, Munich, and Tuebingen for their valuable support. This study was supported by a collaborative grant from the German Cancer Aid (Deutsche Krebshilfe, 70-3163-Wi3) within the framework of the grant *German Glioma Network.*

Funding:

This study was supported by a collaborative grant from the German Cancer Aid (Deutsche Krebshilfe, 70-3163-Wi3) within the framework of the grant German Glioma Network

Disclosures:

Ma. W. Served on scientific advisory boards for Roche, Neurofluidics, BioMarin and PharmocoKinesis, received an honorarium from Eizai Pharmaceuticals and received royalties from the publication of the book *Oncology of CNS Tumors*

G. R. Served on the advisory board for Merck Serono.

Mi. W. Received honorary for participation in Speakers' Bureaus and Advisory Boards for MSD, Roche, Antisense Pharma, Merck Serono, and has received funding for research from Roche, Merck Serono, Antisense Pharma and Bayer.

J.-C. T. Received honoraria for serving on the scientific advisory boards of Merck Serono and Roche and received royalties from the publication of the book *Oncology of CNS Tumors*.

All remaining authors have declared no conflicts of interest

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Figure legends:

Figure 1: (A) PFS and (B) OS by extent of resection of the overall population. (C) PFS and (D) OS by *MGMT* promoter methylation status of the overall population. (IR, incomplete resection; GTR, gross total resection)

Figure 2: (A) PFS and (B) OS by extent of resection for the RT plus CT subpopulation. (C) PFS and (D) OS by *MGMT* promoter methylation status for the RT plus CT subpopulation. (CT, chemotherapy; GTR, gross total resection; IR, incomplete resection; RT, radiotherapy)

Figure S1: (A) PFS and (B) OS by treatment for the overall population. (CT, chemotherapy, RT, radiotherapy)

Figure S2: (A) PFS and (B) OS by both extent of resection and *MGMT* promoter methylation status for the overall population. (GTR, gross total resection; IR, incomplete resection)

Contributions:

F.-W. K. Study concept and design, analysis and interpretation of the data, drafting and revising the manuscript for intellectual content

N. T. Study concept and design, analysis and interpretation of the data, drafting and revising the manuscript for intellectual content

S. M. Study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content

Ma. W. Study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content

G. S. Study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content

N. G. Study concept and design, acquisition of the data, critical revision of the manuscript for important intellectual content

B. H. Statistical analysis and interpretation of the data, critical revision of the manuscript for important intellectual content

G. R. Study concept and design, acquisition of the data, critical revision of the manuscript for important intellectual content

T. P. Study concept and design, acquisition of the data, critical revision the manuscript for important intellectual content

Mi. W. Study concept and design, analysis and interpretation of the data, drafting and revising the manuscript for intellectual content

J.-C. T. Study concept and design, analysis and interpretation of the data, drafting and revising the manuscript for intellectual content

Previous presentations:

This study was presented in part (as oral presentations) at the 10th Meeting of the European Associaton of NeuroOncology (EANO), September 6-9, 2012, in Marseille, France, and at the 2012 Annual Meeting of the Society for NeuroOncology (SNO), November 15–18, 2012, Washington, DC, USA.

Supplement Table S1: Univariate analyses for the overall population

PFS			
	Hazard ratio	**95% CI**	***p* value**
Age ≤ 60 vs. > 60	0.56	0.45-0.70	<0.001
KPS ≥ 80 vs. < 80	0.67	0.51-0.87	0.002
MGMT meth. vs. unmeth.	0.56	0.44-0.67	<0.001
Extent of resection			
IR vs. biopsy (ref.)	0.88	0.66-1.12	0.410
GTR vs. biopsy (ref.)	0.73	0.54-0.99	0.045
Treatment			
RT or CT vs. pall. (ref.)	0.27	0.18-0.40	<0.001
RT plus CT vs. pall. (ref.)	0.17	0.12-0.25	<0.001
OS			
	Hazard ratio	**95% CI**	***p* value**
Age ≤ 60 vs. > 60	0.47	0.37-0.59	<0.001
KPS ≥ 80 vs. < 80	0.53	0.41-0.70	<0.001
MGMT meth. vs. unmeth.	0.43	0.34-0.55	<0.001
Extent of resection			
IR vs. biopsy (ref.)	0.77	0.57-1.04	0.090
GTR vs. biopsy (ref.)	0.55	0.40-0.75	<0.001
Treatment			
RT or CT vs. pall. (ref.)	0.30	0.20-0.45	<0.001
RT plus CT vs. pall. (ref.)	0.15	0.11-0.22	<0.001

Legend: CT, chemotherapy; GTR, gross total resection; IR, incomplete resection; KPS, Karnofsky performance score; *MGMT*, O^6-methylguanine-DNA

methyltransferase; meth., methylated promoter status; unmeth, unmethylated promoter status; pall., palliative care; RT, radiotherapy, vs., versus

Table 1. Summary of patients' characteristics.

	All patients (*N*=345)	
Age at diagnosis (years)		
Median	61	
Range	19-86	
Age classes	*N*	*%*
≤50 years	85	24.6
51-60 years	83	24.1
61-70 years	115	33.3
>70 years	62	18.0
Gender	*N*	
Male	209	60.6
Female	136	39.4
KPS	*N*	*%*
90-100	146	43.2
70-80	164	48.5
<70	28	8.3
No data	7	-
Surgery	*N*	*%*
Gross total resection	125	36.2
Incomplete resection	148	42.9
Biopsy	72	20.9
Review diagnosis	*N*	*%*
Glioblastoma	329	95.4
Giant cell glioblastoma	9	2.6

Gliosarcoma	7	2.0
***MGMT* promoter methylation status**	*N*	*%*
Methylated	163	48.1
Unmethylated	176	51.9
Unknown	6	-
Therapy	*N*	*%*
First-line		
Supportive care	39	11.3
RT alone	69	20.0
CT alone[1]	15	4.3
RT plus CT[2]	222	64.3
Second-line (*N*=161)		
Surgery alone	26	16.1
Surgery plus CT	44	27.3
Surgery plus RT plus CT	9	5.6
RT alone	2	1.2
RT plus CT	21	13.0
CT alone	59	36.6

Legend: CT, alkylating chemotherapy; RT, radiation therapy; [1], TMZ (*N*=13) or nitrosourea (*N*=2); [2], concomitant plus adjuvant TMZ (*N*=164), concomitant TMZ only (*N*=42), adjuvant TMZ only (*N*=12), nitrosourea (*N*=4), one dose was sufficient to place a patient in this group, non-alkylating agents were excluded, no patient received first-line bevacizumab.

Table 2: Outcome of patients stratified for extent of resection, *MGMT* promoter methylation status and treatment regimes.

	All patients		**Gross total resection**		**Incomplete resection**		**Biopsy**	
PFS	**Median (95%CI)**	**Event**	**Median (95%CI)**	**Event**	**Median (95%CI)**	**Event**	**Median (95%CI)**	**Event**
Palliative care	2.7 (1.0-3.5)	36/39	0.7 (0.4-1.0)	8/8	2.2 (0.9-3.5)	17/17	2.4 (1.3-3.4)	11/14
RT alone	6.6 (5.9-7.3)	67/69	6.7 (5.8-7.5)	23/24	6.8 (5.3-8.2)	33/33	4.5 (2.3-6.6)	11/12
CT alone	2.4 (1.3-3.5)	14/15	-	1/1	-	4/4	2.9 (0.02-5.8)	9/10
RT plus CT	7.8 (6.6-9.0)	210/222	7.8 (4.8-10.8)	88/92	7.4 (6.2-8.5)	91/94	8.8 (4.3-13.4)	31/36
Total	6.4 (5.7-7.1)	327/345	6.7 (5.7-7.7)	120/125	6.5 (5.7-7.3)	145/148	4.6 (3.1-6.0)	62/72
Patients with *MGMT* promoter methylation								
Palliative care	1.7 (0.5-3.0)	17/18	-	4/4	2.3 (2.0-2.7)	7/7	-	6/7
RT alone	5.4 (2.9-7.9)	28/30	5.1 (3.5-6.6)	10/11	7.5 (6.6-8.4)	15/15	-	3/4
CT alone	2.9 (0.8-5.0)	8/9	-	0/0	-	0/0	2.9 (0.8-5.0)	8/9
RT plus CT	13.2 (9.8-16.6)	97/106	15.0 (12.3-17.7)	41/45	9.0 (3.7-14.3)	44/46	12.0 (8.7-15.2)	12/15
Total	7.6 (6.0-9.1)	150/163	10.2 (1.8-18.6)	55/60	7.6 (6.3-8.8)	66/68	4.1 (0.6-7.6)	29/35
Patients without *MGMT* promoter methylation								
Palliative care	3.0 (0.2-5.8)	19/21	-	4/4	-	10/10	-	5/7
RT alone	6.6 (5.3-7.8)	36/36	7.3 (5.3-9.3)	11/11	6.2 (6.0-6.4)	18/18	-	7/7
CT alone	-	6/6	-	1/1	-	4/4	-	1/1
RT plus CT	6.4 (5.5-7.3)	110/113	5.7 (4.5-6.9)	46/46	6.8 (6.3-7.3)	47/48	7.3 (1.7-12.9)	17/19
Total	5.8 (5.0-6.6)	171/176	6.4 (5.2-7.5)	62/62	6.1 (4.8-7.5)	79/80	4.7 (3.9-5.4)	30/34
OS	**Median (95%CI)**	**Event**	**Median (95%CI)**	**Event**	**Median (95%CI)**	**Event/n**	**Median (95%CI)**	**Event**
Palliative care	3.0 (1.4-4.6)	36/39	0.9 (0-4.8)	8/8	2.4 (0-4.9)	17/17	3.0 (0.6-5.5)	11/14
RT alone	9.6 (8.4-10.8)	65/69	12.4 (4.2-20.5)	22/24	8.8 (7.1-10.6)	32/33	4.7 (3.5-6.0)	11/12
CT alone	6.2 (3.4-9.0)	15/15	-	1/1	-	4/4	6.2 (2.3-10.1)	10/10
RT plus CT	17.1 (14.5-19.6)	194/222	21.0 (18.9-23.1)	81/92	15.2 (11.8-18.4)	83/94	15.7 (10.1-21.3)	30/36
Total	12.8 (11.2-14.4)	310/345	17.1 (12.6-21.5)	112/125	11.7 (10.0-13.5)	136/148	8.7 (6.3-11.2)	62/72
Patients with *MGMT* promoter methylation								
Palliative care	2.3 (1.5-3.2)	17/18	-	4/4	-	7/7	-	6/7
RT alone	9.9 (8.5-11.3)	27/30	9.6 (6.9-12.4)	9/11	10.1 (5.9-14.2)	15/15	-	3/4
CT alone	6.2 (0.1-12.4)	9/9	-	0/0	-	0/0	6.2 (0.1-12.4)	9/9
RT plus CT	27.5 (22.4-32.6)	83/106	33.2 (17.6-48.9)	35/45	24.4 (19.2-29.6)	37/46	26.2 (17.7-34.6)	11/15

Total	21.0 (15.9-26.1)	136/163	25.2 (18.3-32.1)	48/60	17.9 (8.1-27.8)	59/68	11.6 (3.6-19.6)	29/35
Patients without *MGMT* promoter methylation								
Palliative care	3.4 (1.6-5.1)	19/21	-	4/4	0.8 (0.1-1.6)	10/10	-	5/7
RT alone	8.7 (8.0-9.5)	35/36	16.9 (9.0-24.7)	11/11	7.1 (3.3-10.9)	17/18	-	7/7
CT alone	-	6/6	-	1/1	-	4/4	-	1/1
RT plus CT	12.8 (11.7-13.8)	108/113	14.4 (12.3-16.5)	45/46	12.6 (11.4-13.7)	46/48	9.8 (6.4-13.3)	17/19
Total	11.0 (9.6-12.4)	168/176	13.9 (12.1-15.8)	61/62	9.7 (7.9-11.5)	77/80	7.7 (4.4-10.8)	30/34

Legend: CT, alkylating chemotherapy; RT, radiation therapy; *MGMT*, O^6-methylguanine-DNA methyltransferase

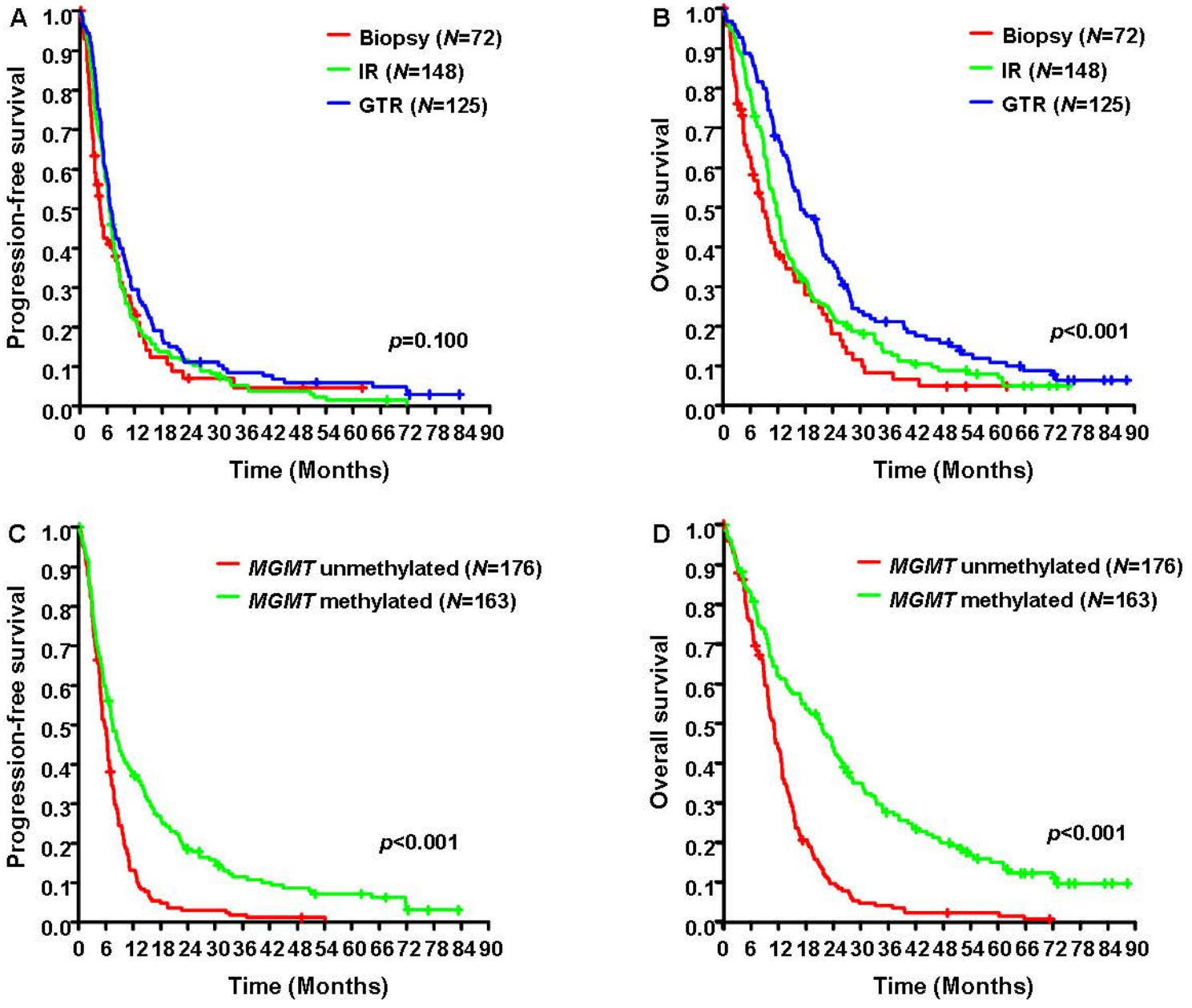

A
Progression-free survival
Biopsy (N=72)
IR (N=148)
GTR (N=125)
p=0.100
Time (Months)
B
Overall survival
Biopsy (N=72)
IR (N=148)
GTR (N=125)
p<0.001
Time (Months)
C
Progression-free survival
MGMT unmethylated (N=176)
MGMT methylated (N=163)
p<0.001
Time (Months)
D
Overall survival
MGMT unmethylated (N=176)
MGMT methylated (N=163)
p<0.001
Time (Months)

Figure 1

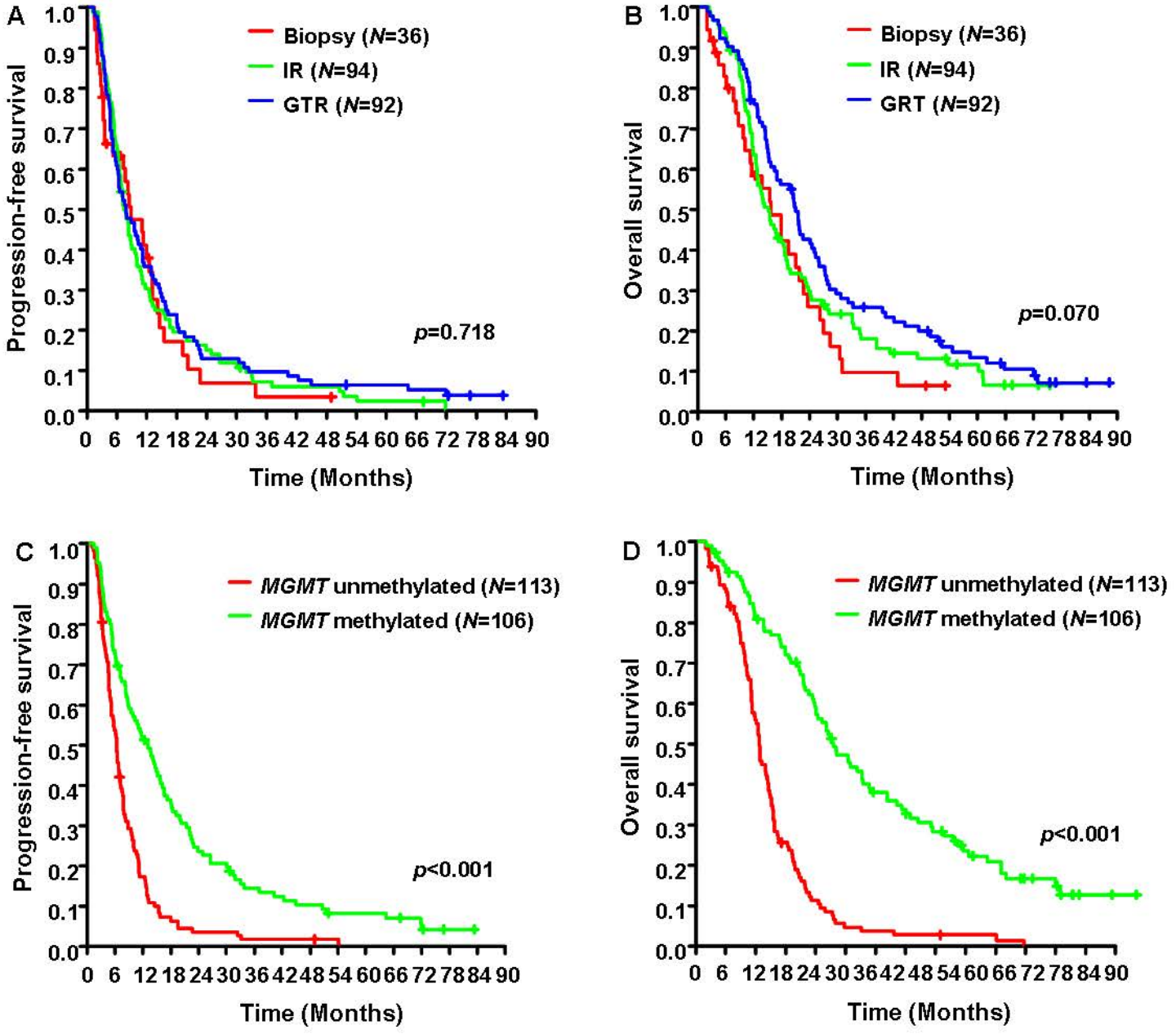
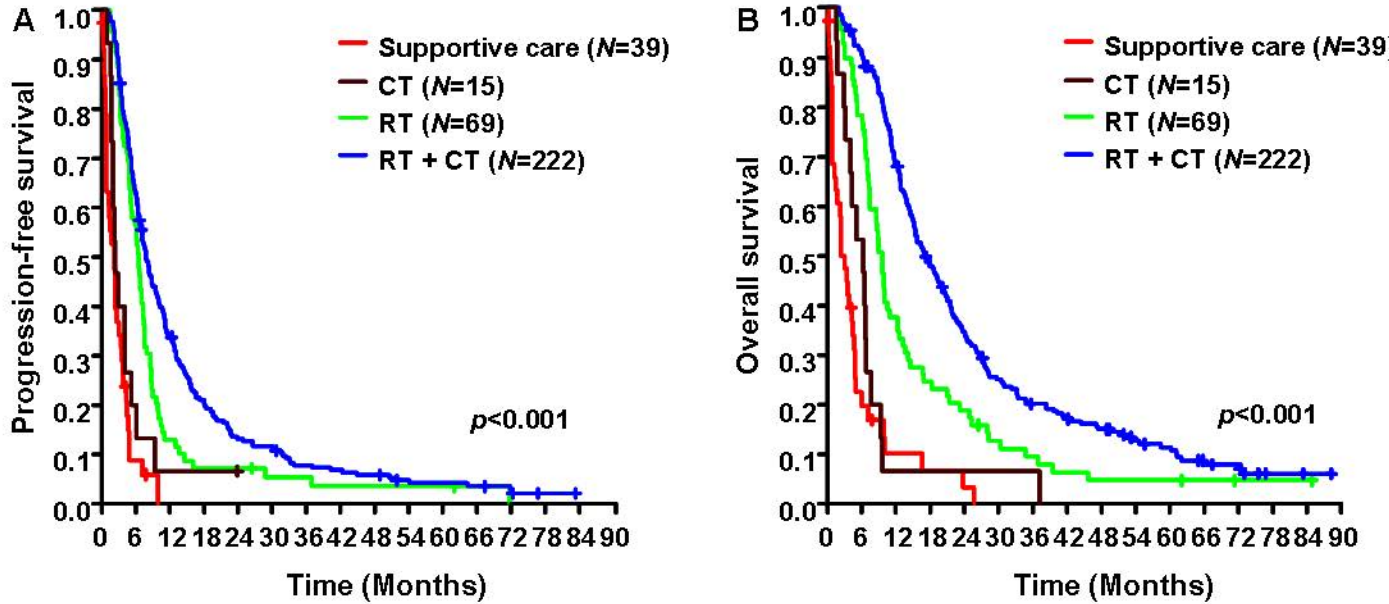
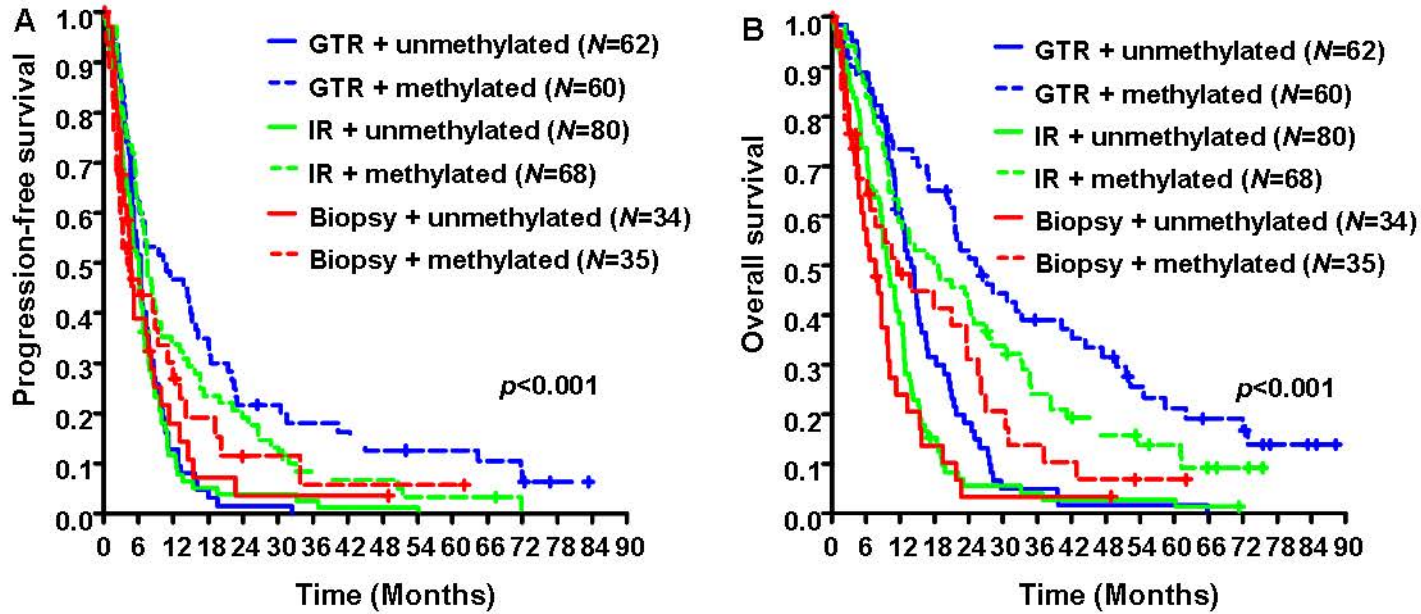

A
Progression-free survival
Biopsy (N=36)
IR (N=94)
GTR (N=92)
p=0.718
Time (Months)
B
Overall survival
Biopsy (N=36)
IR (N=94)
GRT (N=92)
p=0.070
Time (Months)
C
Progression-free survival
MGMT unmethylated (N=113)
MGMT methylated (N=106)
p<0.001
Time (Months)
D
Overall survival
MGMT unmethylated (N=113)
MGMT methylated (N=106)
p<0.001
Time (Months)

Figure 2



Supplement Figure S1



Supplement Figure S2